2. SCIENTIFIC ABSTRACT

The proposed study is a Phase 1/2 trial to evaluate an adenovirus construct expressing P501 protein (Ad/P501) and a recombinant P501 protein (CPC-P501) plus adjuvant (AS15) as an immunotherapeutic vaccine strategy in patients with prostate cancer. The primary objective of this trial is to determine the safety of a vaccine regimen consisting of Ad/P501 followed by CPC-P501/AS15 with dose-escalation of the Ad/P501 component of the vaccine regimen through three cohorts in patients with prostate cancer who have a prostate-specific antigen (PSA) level ≥ .04 ng/mL and no other evidence of disease following radical prostatectomy. Additionally, this trial will assess the extent to which antibody and/or cell-mediated immunity (CD4+ and/or CD8+ T cells) specific for the P501 protein will be elicited by this vaccine regimen.

The Ad/P501 – CPC-P501/AS15 immunotherapeutic vaccine targets a prostate cancer-associated protein in order to prevent recurrence. The immunogenic protein is termed P501. The vaccine product contains two components, a recombinant adenovirus-5 containing the P501 gene (Ad/P501) and a recombinant protein with an adjuvant (CPC-P501/AS15, GSK Biologicals). Ad/P501 is designed to initiate a CD8+ T cell response to the P501 protein, which is highly expressed in prostate cancer. CPC-P501/AS15 will be used to expand the CD8+ response and elicit both a CD4+ T cell response as well as an antibody response to the P501 antigen.

The rationale for the use of both adenovirus and recombinant protein as immunizing agents is the desire to elicit a strong, comprehensive immune response including CD8+ T cells (cytotoxic T lymphocytes-CTL), CD4+ T cells (helper T cells), and antibody. Standard vaccine methods for inducing CTL to prostate proteins/antigens have not been established. Administering an adenovirus construct containing the P501 gene should allow the antigen to be presented through the class I MHC antigen processing pathway resulting in the generation of CTL. A subsequent administration of recombinant protein plus adjuvant will be used to elicit CD 4+ T cells and antibody responses.

The proposed clinical protocol is a Phase 1/2 open-label, safety and immunogenicity study of Ad/P501, with doses escalating through three cohorts, followed by a fixed dose of CPC-P501/AS15 in patients with prostate cancer who have PSA level ≥ .04 ng/mL after radical prostatectomy. The Ad/P501 and CPC-P501/AS15 will be administered separately by intramuscular (IM) injection at separate time points.

For the Phase 1 component of the clinical study, six cancer patients will be enrolled in each of three cohorts in the study. Ad/P501 injections will be administered on Days 0 and 14; Ad/P501 doses will be escalated from 1 x 10^{10} viral particles (vp) in Cohort 1, through 1 x 10^{11} vp in Cohort 2 to 1 x 10^{12} vp in Cohort 3. All subjects will receive the same dose of CPC-P501/AS15 (100 µg CPC-P501) on Days 35, 56 and 77. The Phase 1 component of the trial is designed to evaluate the maximum tolerated dose (MTD) of the vaccine regimen. If the vaccine dose level for all three cohorts is safe and an MTD is not exceeded/determined, no further dose escalation will occur and the Phase 2 component of the trial will further evaluate the safety profile at the Cohort 3 dose level.

After completion of the Phase 1 component of the study, a Phase 2 component of the trial will use a two-stage design to further evaluate safety, immunogenicity and changes in PSA levels. In the first stage, an additional 35 subjects will be enrolled at the MTD (or Cohort 3) dose level

resulting in a total of 41 subjects at that dose level. If more than 20 of the 41 subjects have an immune response, the immune response rate will be deemed adequate to further assess for changes in PSA levels and enrollment will continue. An additional 23 subjects will be enrolled at the MTD (or Cohort 3) dose level during this second stage (a total of 64 subjects at that dose level).